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TITLE: Permethrin Exposure Dosimetry: Biomarkers and Modifiable Factors

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14. ABSTRACT

The primary aim of this project is to investigate the relationship between various modifiable factors and the absorption of permethrin as a result of wearing permethrin-treated Army Combat Uniforms (ACU-Permethrin). The research objective is to examine the effect of body weight/BMI and total energy expenditure on permethrin absorption and dose, as determined by measurement of urinary biomarkers (3PBA and cis- and trans-DCCA) levels. There are two studies involved in our project – the first is a study among Army recruits during Basic Training (Study 1) and the second involves Army National Guard Soldiers during Annual Training (Study 2). Data collection for Study 1 and for Study 2 was completed in 2015 and 2017 respectively. Data analyses and manuscript preparations are in progress.

15. SUBJECT TERMS
Permethrin, biomarkers, military, dose, exposure dosimetry, military, energy expenditure

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Section 1: Introduction

The primary aim of this project is to investigate the relationship between various modifiable factors and the absorption of permethrin as a result of wearing permethrin-treated Army Combat Uniforms (ACU-Permethrin). The research objective is to examine the effect of body weight/BMI and total energy expenditure on permethrin absorption and dose, as determined by measurement of urinary biomarkers (3PBA and cis- and trans-DCCA) levels. There are two studies involved in our project – the first is a study among Army recruits during Basic Training (Study 1) and the second involves Army National Guard Soldiers during Annual Training (Study 2).

Section 2: Keywords

Permethrin, biomarkers, military, dose, exposure dosimetry, military, energy expenditure

Section 3: Accomplishments

3:1 - What were the major goals of the project?

As described in the approved Statement of Work (see Table of Tasks below), the major goals during the Year 3 of this project are outlined (see blue highlighted Task sections below).

TASKS 1-3 were completed in Year 1 (See Year 1 Annual Report.)
TASKS 4-10, 12, and 14 were completed in Year 2 (See Year 2 Annual Report.)

Year 1	***Task 1***	*Months 1-4*	-Project set up and approvals
	Task 2	*Months 4-8*	-Plan logistics for Study 1
	Task 3	*Months 4-8*	-Study 1 protocol approval
	Task 4	*Months 8-12*	-Initiate Study 1 data collection
	Task 5	*Months 10-12*	-Initiate laboratory analyses of Study 1 samples
	Task 6	*Months 10-12*	-Initiate Study 1 data management steps; integrate with USARIEM research database system
Year 2	***Task 7***	*Months 13-15*	-Prepare analytic dataset for data analyses
	Task 8	*Months 15-17*	-Initiate Study 1 data analyses to address hypotheses
	Task 9	*Months 14-20*	-Plan logistics for Study 2
	Task 10	*Months 14-20*	-Study 2 protocol approval
	Task 11	*Months 16-24*	-Report/summarize Study 1 results
	Task 12	*Months 20-24*	-Initiate Study 2 data collection
Year 3	***Task 13***	*Months 25-26*	-Initiate laboratory analyses of Study 2 samples
	Task 14	*Months 25-30*	-Initiate Study 2 data management steps

	Task 15	*Months 30-36*	-Complete Study 1 and Study 2 laboratory sample analyses
Year 4	***Task 16***	*Months 37-39*	-Complete integration of analytic dataset for project data analyses
	Task 17	*Months 37-39*	-Complete Study 2 data analyses to address hypotheses
	Task 18	*Months 39-48*	-Report/summarize Study 2 results -Prepare Project technical reports/manuscripts for publication
	Task 19	*Months 39-48*	-Provide/disseminate evidence-based guidance

3:2 - What was accomplished under these goals?

Below is a bulleted list of the projected goals and accomplishments over this Year 3 study period:

Task 11 *Report/summarize Study 1 results* [**IN PROGRESS**]

- Preliminary analyses to address the Study 1 hypotheses are complete.

  Summary of Study 1 conducted among Active Duty Army recruits**.** The age range of the 60 participants was between 18-29.5 years and the average age was 21.3 years old. Thirty percent of the group was female. Among the 44 persons who completed all aspects of the longitudinal study, baseline percent body fat (% BF) was 14.72%, and the average % BF decreased 2.83 % (males decreased 3.16%; females decreased 2.13%) by the end of the study (10 week period of Basic Combat Training (BCT)). The highest level of urinary permethrin metabolites were observed during week 1 of BCT, which makes intuitive sense as the uniforms worn were new with limited washing. A significant correlation ($r= -0.52$, $p <0.0001$) between measured levels and number of times the uniform had been washed was observed. Mixed models were run to examine the hypothesis of whether permethrin exposure/absorption was associated with % BF. A total of 274 observations were made from n=51 total participants (who met creatinine concentration criteria). Analyses show that 10% higher % BF is statistically associated with a 3.43% higher concentration of 3-phenoxybenzoinc acid, a permethrin metabolite; ($F = 16.16$, $p < 0.0001$). This association holds after controlling for known confounders including sex, age, time that uniform was worn, times uniform was washed, and the duration of time in BCT.

- A presentation abstract was submitted and accepted for presentation at the Annual American Public Health Association meeting in Atlanta in Nov 2017. (Abstract is provided in the Appendix.)

- A manuscript describing Study 1 results is under preparation.

Task 12 *Initiate Study 2 data collection* [**COMPLETE**]

- Study 2 data collection with the MA ARNG was initiated in June 2016, with a total of n=15 providing consent and n=14 persons participants completing the study.
- Data collection efforts for Study 2 with the ME ARNG were completed in early August (4-12 Aug 2016) with a total of n=14 participants consenting and completing the study.
- Data collection efforts for Study 2 with the MA ARNG were completed in early June (7-15 June 2017) with a total of n=21 participants consenting and n=19 completing the study.
- In total for Study 2, 50 persons provided consent and 47 persons completed the study.

Task 13 *Initiate laboratory analyses of Study 2 samples* [**COMPLETE**]

- All laboratory analyses of the Study 2 samples collected in 2016 at CDC and PBRC have been completed. Sample analyses for the June 2017 data collection have been submitted to CDC and PBRC for analyses.

Task 14 *Initiate Study 2 data management steps* [**COMPLETE**]

- Data management steps, in terms of setting up the data collection instruments/surveys for Study 2 and making a plan for the integration of collected data into a study database has been completed.

Task 15 *Complete Study 1 and Study 2 laboratory sample analyses* [**~90% COMPLETE]**

- ~90% of all sample analyses by PBRC and CDC are complete; we anticipate receipt of all sample analyses results by Oct 2017.

3:3 - What opportunities for training or professional development has the project provided?

- A Boston University School of Public Health graduate student (MPH candidate) has worked on this project; her primary role on the project is performing data management and analytic tasks for the project. She graduated with her MPH in Dec 2016.

- A Boston University School of Public Health graduate student (PhD candidate) is currently working on this project; her primary role on the project is to help direct field data collection activities and in preparation of reports, abstract, manuscripts, and presentations. She graduated with her PhD in May 2017.

3:4 - How were [are] the results [being] disseminated to communities of interest?

- As results become available from this project, continued updating and presentation of study results are planned for upcoming national conferences, as well as direct briefings to DoD stakeholders (i.e., USA Training and Doctrine Command, Federal and State National Guard stakeholders, Armed Forces Pest Management Board, and US Army Public Health Center).

3:5 - What do you plan to do during the next reporting period to accomplish the goals?

- During the next reporting period, we will
  - prepare and submit of manuscripts for peer-reviewed publications and submit abstracts describing Study 1 and 2 results to national conferences
  - meet and present results to military stakeholders and policy providers (i.e., Armed Forces Pest Management Board (March 2018) and USA Public Health Center (Spring 2018)

Section 4: Impact

4:1 - What was the impact on the development of the principle discipline of the project?

- Nothing to report at this point.

4:2 - What was the impact on other disciplines?

- Nothing to report at this point.

4:3 - What was the impact on technology transfer?

- Nothing to report at this point.

4:4 - What was the impact on society beyond science and technology?

- Nothing to report at this point

Section 5: Changes/Problems

5:1 - Changes in approach and reasons for change

- Nothing to report.

5:2 - Actual or anticipated problems or delays and actions or plans to resolve them

- As of 4 August 2017, we have not received the planned incremental Year 4 funding. We realize that the project funding is subject to available funds, per the award agreement. But, we would appreciate communication about the status of Year 4 funds as this may impact the progress and completion of the project within approved timelines.

5:3 - Changes that had a significant impact on expenditures

- See note above.

5:4 - Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- Nothing to report

Section 6: Products

6:1 - Publications, conference papers, and presentations

- Presentation planned for upcoming APHA meeting Nov 2017: Submitted Abstract (See Appendix A): Effect of body composition on permethrin dose when wearing treated military uniforms during initial military training

6:2 - Websites and/or Internet Sites

- Nothing to report

6:3 - Technologies or techniques

- Nothing to report

6:4 - Inventions, patent applications, and/or licenses

- Nothing to report

6:5 - Other products

- Nothing to report

Section 7: Participants and other Collaborating Organizations

7:1 - What individuals have worked on the project?

- ✓*Name:* Susan P. Proctor, DSc
  Project Role: Principal Investigator
  Nearest person-month worked: 15% of 12 person-months (1.8 person-months)
  Contribution to Project: Handling all PI responsibilities for the project, including interactions with the IRB, the grantee (HJF), CIMT, Army recruit training POCs, Fort Sill, NGB/ARNG, and CDC and PBRC staff.
  Funding Support: Army Civilian employee
- ✓*Name:* Matthew M. Scarpaci, MPH
  Project Role: Project Coordinator
  Nearest person-month worked: 100% of 12 person-months (12 person-months)
  Contribution to Project: Mr. Scarpaci has assumed the role of project coordination, assisting the PI in the day-to-day planning of the project, IRB tracking, HJF administrative tasks, data collection preparations, and data management etc.
- ✓*Name:* Alexis Maule, PhD
  Project Role: Research Associate
  Nearest person-month worked: ~75% of 12 person months (9 person months)
  Contribution to Project: Ms. Maule has continued to assist the PI and project coordinator on IRB-related tasks and training additional study staff on data collection processes.
  Funding Support: Boston University employee supported through USARIEM IPA
- ✓*Name:* Caitlin Dillon, MPH
  Project Role: Data Analyst
  Nearest person-month worked: 50% of 12 months (6 person-months)- started June 2015 (ending late July 2016) 5-10% of 12 months (.5-1 person-months)- started July 2016-June 2017
  Contribution to Project: Ms. Dillon has worked on the set-up of data management tasks and work on database and analyses.
- ✓*Name:* Nicole Murphy, BS
  Project Role: Research Associate
  Nearest person-month worked: 50% of 5 months (2.5 person-month)- May –Oct 2016
  Contribution to Project: Ms. Murphy has assisted in data collection and data entry processes.

7:2 - Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- o Nothing to report

7:3 - What other organizations were involved as partners?

- o Nothing additional to report

Section 8: Special Reporting Requirements

8:1 – See Quad Report

Section 9: Appendices

Abstract: For presentation at the upcoming Annual American Public Health Association meeting in Atlanta in Nov 2017

Quad chart

Title: Effect of body composition on permethrin dose when wearing treated military uniforms during initial military training

Authors: Scarpaci MM, Dillon CC, Maule AL, Taylor KM, Ospina M, Calafat AM, Heaton KJ, Proctor SP

Background: As of 2013, US Army policy requires all new uniforms issued be permethrin-treated for protection against insect bites and vector-borne illnesses. Permethrin is a low-toxicity insecticide with neurotoxicant properties and research demonstrates that body fat may influence dermal absorption. We investigated the effect of percent body fat (%BF) on permethrin absorption among Soldiers wearing permethrin-treated uniforms in a 10-week training period.

Methods: This prospective study involved US Army recruits and three data collection visits occurring during the first, middle, and last week of Basic Combat Training (BCT) period. Individual measurements of %BF (skinfold method) were obtained a total of six times (start and end of each visit). Spot urine samples were collected daily during each visit and analyzed for permethrin metabolites (3-phenoxybenzoic acid, *cis*- and trans-2,2-(dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid) and creatinine. The relationships between %BF and metabolite concentrations were examined via linear mixed modeling. All models were adjusted for creatinine, age, sex, days in BCT, number of times worn uniform was washed, and daily number of hours uniform was worn.

Results: Sixty participants started the study (average age=20.77 years; 30% female); 44 recruits completed the study. For a 10% higher %BF level permethrin metabolites concentrations were 3.43-3.58% higher ($p<0.0001$).

Conclusion: Higher %BF was a significant factor in the absorption of permethrin. The independent effect of body composition will be discussed in relationship to other risk factors including uniform wash history and wear time duration.

Permethrin Exposure Dosimetry: Biomarkers and modifiable factors

Log Number: 13063057 Task Area: Biomarkers to monitor for injury and disease processes

Contract #: W81XWH-14-2-0130

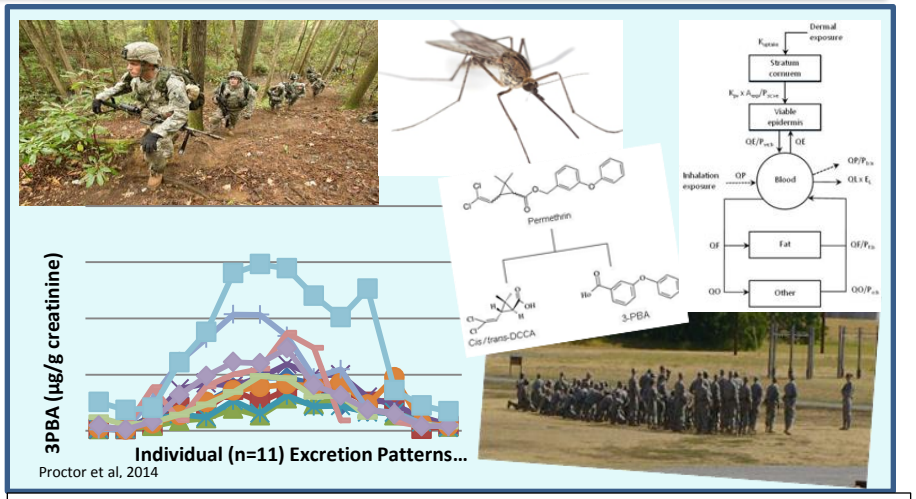
PI: Susan P. Proctor, DSc **Org:** Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) **Award Amount:** $1,861,959

Study/Product Aim(s)

- Address the influence of permethrin exposure from wearing treated uniforms (ACU-Permethrin) on human dose and monitor the potential role of exposure on health and performance for accurate policy guidance regarding potential health risk.
- The study aims to determine the modifiable factors that significantly influence human permethrin dosimetry as a result of wearing the ACU-Permethrin. Specifically, determine whether body weight/body mass index and physical activity patterns influence the absorbed permethrin dose.

Approach

The project will define relationships between ACU-Permethrin wear-time scenarios among Army recruits (at Basic Training, Study 1) and Army National Guard Soldiers (during Annual Training, Study 2), urinary biomarkers of dose (3PBA, cis- and trans-DCCA), and modifiable factors (body mass index and physical activity levels) to provide valid predictive models.



Accomplishments [Yr3]: Study 2 data collection complete (with ARNG); sample analyses are 90% complete and data analyses are in progress. Presentations and manuscripts in progress.

Timeline and Cost

Activities:	**Yr 1** 7/14-6/15	**Yr 2** 7/15-6/16	**Yr 3** 7/16-6/17	**Yr 4** 7/17-6/18
Project Start-Up/Approvals				
Study 1 and Study 2 Data Collection and Sample Analysis				
Data analyses & Preparation of Manuscript & Reports				
Estimated Budget ($K)	**$718**	**$521**	**$307**	**$316**

Updated: 15 July 2017

Goals/Milestones

Yr1 Goals – Study approvals and Initiation of Study 1

☑ USARIEM IRB approval; HRPO approval granted Oct 2014

☑ Complete Study 1 site planning steps and initiate data collection

Yr2 Goals– Initiate Study 1 data analyses and Study 2 data collection

☑ Initiate Study 1 data analyses

☑ Complete Study 2 site planning steps and initiate data collection

Yr3 Goals– Complete Study 2 data collection and sample analyses

☑ Initiate Study 2 data analyses

☑ Complete Study 1 and 2 laboratory sample analyses (90% complete)

Yr4 Goals–Complete data analyses and manuscript(s) preparation

☐ Finalize data analyses and modeling

☐ Prepare technical reports/ manuscript(s)

Comments/Challenges/Issues/Concerns

- None, all on track

Budget Expenditure to Date:

Projected Expenditure: ~$1.5K

Actual Expenditure (as of July 2017): ~$1.2K